REMARKS

Claims 29-48 presently appear in this case. Claims 44 and 45 have been withdrawn from consideration. No claims have been allowed. The Official Action of February 19, 2010, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a pH-independent extended release dosage form of venlafaxine hydrochloride. The venlafaxine hydrochloride is coated on a nonpareil core over which is coated a controlled release layer, which is a hydrophobic polymer optionally mixed with a plasticizer. The controlled release layer permits controlled release of the venlafaxine hydrochloride over an approximately 24 hour period. An intermediate layer of hydrophilic polymeric polymer or glycerol monostearate (GMS) may also be present. Preferably, the pH-independent extended release dosage form has dissolution characteristics that are equivalent to those of the venlafaxine hydrochloride dosage forms sold under the proprietary name EFFEXOR XR.

The examiner has held newly submitted claims 44 and 45 to be directed to an invention that is independent or distinct

from the invention originally claimed, as the original claims were composition claims while claims 44 and 45 pertain to method claims. Accordingly, claims 44 and 45 have been withdrawn from consideration as being directed to a non-elected invention in accordance with 37 CFR 1.142(b) and MPEP §821.03. This restriction requirement is respectfully traversed.

The present application is a national stage application of an international application and is thus subject to unity of invention rules and not U.S. restriction practice. Unity of invention practice is discussed at MPEP 1893.03(d), which refers to the detailed discussion of unity of invention practice at MPEP §1850. Under unity of invention practice, this restriction requirement is improper. Note particularly 37 CFR 1.475(b), which explicitly states that a national stage application will be considered to have unity of invention despite containing claims to different categories of invention if the claims are drawn to "(3) a product, a process specially adapted for the manufacture of said product, and a use of the said product." As claims 44 and 45 are both dependent on claim 31 and are directed to a process of making and a process of use of that product, these claims must be examined together with the

product claims in this case. Accordingly, reconsideration and withdrawal of the restriction requirement and action on all of the claims now present in the case as is required by 37 CFR 1.475(b) are respectfully urged.

The examiner states that the use of the trademark EUDRAGIT has been noted in the specification. The examiner states that it should be capitalized wherever it appears and be accompanied by the generic terminology.

The specification has now been reviewed and so many corrections were deemed necessary that it was thought best to file a substitute specification rather than to make a lengthy correction to the specification paragraph by paragraph. MPEP §608.01(q) states that 37 CFR §1.125(b) applies to a substitute specification voluntarily filed by the applicant. Subject to the provisions of 37 CFR 1.312, a substitute specification, excluding claims, may be voluntarily filed by the applicant at any point up to the payment of the issue fee, provided that it is accompanied by a statement that the substitute specification includes no new matter. Accordingly, attached hereto is a substitute specification in clean form without markings as well as a marked up copy of the substitute specification showing all

of the changes relative to the immediate prior version of the specification of record.

The undersigned hereby states that the substitute specification includes no new matter.

With respect to the trademark noted by the examiner, it can be seen that the substitute specification uses all capital letters for every proprietary name throughout the specification. For EUDRAGIT, please note that paragraph [0008] of the amended specification submitted herewith already has generic terminology for this polymer, i.e., "ammonio methacrylate copolymer, type A or B." The new substitute specification also adds a last paragraph that gives the IUPAC name for the two EUDRAGIT compounds specifically mentioned in the examples. Submitted herewith are the relevant pages from the EUDRAGIT website showing this known terminology for these products. Similarly, the last sentence of the specification clarifies that ETHOCEL is ethylcellulose and METHOCEL is methylcellulose or a methyl cellulose/hydroxypropylmethylcellulose polymer; this complies with the requirement to insert generic names for these products. To show that this is not new matter, submitted herewith is

product information from the Dow Chemical Company on their METHOCEL and ETHOCEL products (note particularly page 6 of the ETHOCEL brochure). Accordingly, applicant has complied with the examiner's requirements with respect to the specification.

Claim 41 has been rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The examiner states that the cellulose derivative lacks chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities.

Claim 41 has now been amended to delete the term "cellulose derivative." The claim now only contains a Markush group of specific compounds. Accordingly, this rejection has now been obviated.

Claims 30, 32, 35, 38 and 41 have been rejected under 35 USC 112, second paragraph, as being indefinite. The examiner states that claims 29 and 32 recite the limitation "GMS" while the specification does not define this term.

The specification has now been amended to specify that GMS is glycerol monostearate. Please see the attached publication prepared at the 17th JECFA (1973); JECFA is the Joint

FAO/WHO Expert Committee on Food Additives. It shows that GMS is a synonym for glycerol monostearate. The claims have now been amended to specify that GMS is glycerol monostearate, thus obviating this part of the rejection.

The examiner states that claim 30 recites a limitation "said additional polymer," while there is insufficient antecedent basis for this limitation in the claim.

Claim 30 has now been amended to delete the term "additional," thus obviating this part of the rejection.

Claims 32, 35 and 38 have been objected to for reciting "comprises GMS or hydrophilic polymer layer," "comprises a binder," and "comprises plasticizer." The examiner states that these limitations might better read "further comprises."

The claims have been amended to change "comprises" to read "further comprises" where appropriate, i.e., where the ingredient mentioned is in addition to an ingredient previously mentioned. Furthermore, the spelling of venlafaxine has been corrected in claim 35. Accordingly, this part of the rejection has now been obviated.

The examiner states that claim 41 contains the trade name EUDRAGIT. The examiner states that the claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. The examiner states that a trademark or trade name is used to identify a source of goods and not the goods themselves.

Claim 41 has now been amended to delete use of the trade name EUDRAGIT or ETHOCEL and to substitute the generic terminology for these trademarks, as supported by the specification (see above discussion). Accordingly, this part of the rejection has now been obviated.

It is noted, however, that a proprietary name has been added to new claim 47. It is urged that this particular use in a claim is not objectionable because the proprietary names used for FDA approved products do indeed identify not only the source of the product but the product itself. Submitted herewith is the "Orange Book" record with respect to this product. The Orange Book is a publication of the U.S. Food and Drug Administration. Note that MPEP §2173.05(u) states that the presence of a trademark or trade name in a claim is not *per se* improper under 35 USC 112, second paragraph.

Claims 29-43 have been rejected under 35 USC 103(a) as being unpatentable over Heiligenstein. The examiner states that it would have been obvious to incorporate venlafaxine in place of duloxetine. The examiner states that the amount of a specific ingredient in a composition is clearly a result-effective parameter that a person of ordinary skill in the art would routinely optimize and that optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. The examiner states that the person of ordinary skill in the art obviously knows that adjustment is necessary since the therapeutic range of duloxetine is 1-30 mg and venlafaxine is 10-150 mg and to meet the bioequivalence requirement of the FDA. This rejection is respectfully traversed.

First of all, it is noted that a nearly identical rejection over the same prior art was made by the present examiner in the Official Action of August 24, 2005, during the earlier prosecution of this case. In applicants' amendment of January 24, 2006, applicants explained to the examiner that the coating of Heiligenstein was an enteric coating while the presently claimed coating was a controlled-release coating and,

therefore, even making the substitutions noted by the examiner, one would end up with an enteric formulation of venlafaxine and not a controlled-release formulation. For these reasons, it was argued that the claimed controlled release formulation could not have been obvious. In the Official Action of April 14, 2006, the examiner stated:

> Applicant's arguments, filed on 01/24/06, with respect to the 35 USC §103 rejection have been fully considered and are persuasive. The 35 USC §103 rejection has been withdrawn.

The examiner, in reinstituting this rejection, has not explained why applicant's arguments that had previously been considered to be persuasive are no longer considered to be persuasive. Thus, reinstitution of this previously withdrawn rejection is inappropriate.

With respect to the merits of the rejection, the examiner's attention is invited to the attached declarations under 37 CFR §1.132 of Dr. Michael Grimshaw and Dr. Yoram Sela. Dr. Grimshaw is an expert in the field of pharmaceutical chemistry and is a consultant with respect to drug delivery technologies in solid dosage forms (see the second paragraph on page 1 of the Grimshaw declaration). Dr. Grimshaw, in reviewing

the examiner's rejection and the Heiligenstein publication, notes (in the paragraph bridging pages 3 and 4) that, while Heiligenstein is not a formulation patent, it does disclose an example of a duloxetine enteric formulation comprising a duloxetine layer over a core bead. The formulation includes an enteric layer of hydroxypropylmethylcellulose acetate succinate (HPMCAS). Dr. Grimshaw points out that this formulation is referred to as an "enteric formulation." throughout Heiligenstein. In this regard, the examiner's attention is invited to paragraph [0010], first sentence, of Heiligenstein as well as paragraph [0012].

At page 4 of his declaration, Dr. Grimshaw refers to the well known definition of "enteric formulation" such as that in Dorland's Illustrated Medical Dictionary 29th Edition, 2000, page 599, which defines "enteric-coated" as designating a special coating applied to tablets or capsules which prevents release and absorption of their contents until they reach the intestines. Dr. Grimshaw testifies that enteric coatings prevent the release at the acid pH conditions of the stomach but permit quick and immediate release under the pH conditions of the small intestine.

In the second paragraph on page 4 of his declaration, Dr. Grimshaw states that his reading of the present application shows that the dosage form thereof is not an enteric formulation but is what is known in the pharmaceutical formulation industry as an "extended-release formulation." He points out that the term "extended-release" is defined in the same Dorland's Illustrated Medical Dictionary, at page 636, as allowing a two-fold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form. Thus, Dr. Grimshaw explains in the paragraph bridging pages 4 and 5 of his declaration, that for an enteric coated formulation, the enteric coating gets the tablets or capsules through the stomach and as soon as they get to the intestine, they are immediately released because of the pH change. Extended release tablets have a different mechanism of release in that release is controlled by diffusion through the coating membrane. In other words, it is not pH-dependent.

In the first full paragraph on page 5 of his declaration, Dr. Grimshaw notes that paragraph [0010] of Heiligenstein indicates that the active ingredient of the enteric layer is HPMCAS. Dr. Grimshaw explains that those of

ordinary skill in the art of drug formulation are well aware that HPMCAS is a completely distinct chemical from hydroxypropylmethylcellulose.

With regard to the examiner's optimization arguments, Dr. Grimshaw notes, in the paragraph bridging pages 5 and 6 of his declaration, that a person of ordinary skill in the art seeking to substitute venlafaxine for duloxetine in the enteric formulation of Heiligenstein would optimize for optimal enteric characteristics as this is what Heiligenstein seeks. Completely changing the ingredients and the amounts so as to obtain a pH-independent formulation with extended release would not be optimization of anything taught by Heiligenstein with respect to enteric-coated formulations. To the contrary, it would be for a purpose which is nowhere mentioned in Heiligenstein.

The declaration of Dr. Sela relates to experimentation conducted by him or in his laboratory under his direct supervision. Dr. Grimshaw analyzes the results of that experimentation, in the paragraph bridging pages 6 and 7 of his declaration, and points out that Figure 1 of the results clearly establishes that the enteric-coated formulation that one obtains when substituting venlafaxine for duloxetine provides a

composition that substantially prevents the release in gastric buffer, pH 1.2, while permitting substantially total release within 1 hour in intestinal buffer, pH 6.8. Dr. Grimshaw points out that this is clearly not pH-independent and shows no extended release characteristics whatsoever. On the other hand, as discussed in the first full paragraph on page 7, the compound made in accordance with the present application showed controlled release over 24 hours, as seen by the Figure 2, which shows release characteristics that are independent of pH and RPM. Figure 2 shows that the results at the gastric pH (1.2) are substantially identical to the results at intestinal pH (6.8). Dr. Grimshaw points out that Figure 3 shows that the dissolution profile of the compounds of the present application are substantially identical, and certainly equivalent, to the release characteristics of EFFEXOR XR, which is made by a totally different process.

In the paragraph bridging pages 7 and 8 of his declaration, Dr. Grimshaw concludes that one of ordinary skill in the art would understand that no "optimization" of the conditions of Heiligenstein would change the pH-dependent dissolution characteristics of the enteric formulation intended

by Heiligenstein to the pH-independent dissolution characteristics provided by the compositions of the present application and that therefore the presently claimed formulation would not have been obvious to anyone of ordinary skill in the art reading Heiligenstein.

In order to make more explicit the differences between the extended release formulation of the present invention as compared to the enteric formulation of Heiligenstein, all of the independent claims have now been amended to recite that the extended release dosage form is "pH-independent." This is supported by paragraph [0013] of the attached amended specification. Clearly, as shown by Figure 1 of the Sela declaration, an enteric coated formulation is not pH-independent; it is quite the opposite. The present specification states that the presently claimed formulation is pH-independent and this is also supported by the examples shown in Figure 2 of the Sela declaration.

Another claimed feature which is not made obvious by Heiligenstein is the statement in the last paragraph of claim 29 that the controlled release layer permits controlled release of the venlafaxine hydrochloride over an approximately 24 hour

period. See the first sentence of paragraph [0009] and the last sentence of [0010] of the attached amended specification. Claim 31 does not use the 24 hour parameter but requires that the hydrophobic polymer layer enable controlled release of the venlafaxine hydrochloride over an extended time period. This is not the case with Heiligenstein, regardless of whether venlafaxine hydrochloride is substituted for duloxetine.

New claim 47 specifies that the dosage form is pH-independent and extended release and that the parameters are selected so as to control release of the venlafaxine hydrochloride over an approximately 24 hour period. However, the claim goes on to specify further that the dissolution characteristics are such as to be equivalent to the dissolution characteristics of EFFEXOR XR; see paragraphs [0014] and [0030] of the attached amended specification. It certainly would not have been predictable or obvious that such would have been possible using a substantially different preparation method from that used to make EFFEXOR XR. .

Accordingly, the claims, particularly as presently amended, clearly define over the enteric formulation of Heiligenstein. Even if venlafaxine hydrochloride was

substituted for duloxetine and "optimized," one would still end up with an enteric formulation that was pH-dependent and would not cause extended release over a period of 24 hours or over an extended period of time. For all of these reasons, as supported by the attached declarations, reconsideration and withdrawal of this rejection are respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 USC §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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